Regarding "C-reactive protein (CRP) elevation in patients with abdominal aortic aneurysm"

Badger et al[1] demonstrated in their case-control study that C-reactive protein (CRP) concentration was higher in patients with abdominal aortic aneurysm (AAA) than that in subjects without AAA (385.0 μL/dL [95% confidence interval, 310.4-442.8] vs 18.03 μL/dL [168.1-196.9]). It has been, however, controvertible whether higher CRP concentration is associated with AAA presence. To summarize the present evidence for an association between CRP and AAA presence, we performed a meta-analysis of case-control studies that compared CRP concentration between patients with AAA and subjects without AAA.

Our comprehensive search identified six case-control studies[1-6] that compared CRP concentration between patients with AAA and patients without AAA. In total, our meta-analysis included data on 744 cases with AAA and 1,288 controls without AAA. Pooled analysis of the six studies demonstrated significantly higher CRP concentration in the AAA group than that in the control group in random-effect models (pooled standardized mean difference [SMD], 0.50; 95% confidence interval [CI], 0.09 to 0.91; $P = .02$) (Fig). There was significant study heterogeneity of results analyzed by means of standard χ^2 tests ($P < .00001$) and accordingly a little difference in the pooled result from fixed-effects modeling (pooled SMD, 0.36; 95% CI, 0.27 to 0.46; $P < .00001$). Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled SMD estimates for the remaining studies. Exclusion of the study by Dawson et al[3] (pooled SMD, 0.54; 95% CI, 0.08 to 0.99; $P = .02$), Golledge et al[4] (pooled SMD, 0.60; 95% CI, 0.13 to 1.07; $P = .01$), Wanhainen et al[5] (pooled SMD, 0.60; 95% CI, 0.13 to 1.07; $P = .01$), or Powell et al[6] (pooled SMD, 0.47; 95% CI, 0.02 to 0.93; $P = .04$) from the analysis did not substantively alter the overall result of our analysis. Meanwhile, eliminating the study by Badger et al[1] (pooled SMD, 0.48; 95% CI, −0.11 to 1.07; $P = .11$) or Alberto et al[2] (pooled SMD, 0.30; 95% CI, −0.02 to 0.62; $P = .07$) substantially changed the pooled point estimate (no significant difference between CRP concentration in the AAA and control group). There was no evidence of significant publication bias using an adjusted rank-correlation test ($P = .0909$).

The results of our analysis suggest that CRP concentration in patients with AAA may be higher than that in patients without AAA, though several sensitivity analyses substantially changed the pooled point estimate. Despite the results of the present meta-analysis and the study by Badger et al,[1] however, further studies may be needed to confirm whether higher CRP concentration is associated with AAA presence.

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REFERENCES

1. Badger SA, Soong CV, O'Donnell ME, Mercer C, Young IS, Hughes AE. C-reactive protein (CRP) elevation in patients with abdominal aortic aneurysm is independent of the most important CRP genetic polymorphism. J Vasc Surg 2009;49:178-84.
2. Alberto P, Maddalena G, Giuseppe G, Ilaria Q, Franci B, Campagna MS, et al. Prevalence of risk factors, coronary and systemic atherosclerosis in abdominal aortic aneurysm: comparison with high cardiovascular risk population. Vasc Health Risk Manag 2008;4:877-83.
3. Dawson J, Cockerill GW, Choke E, Belli AM, Loftus I, Thompson MM. Aortic aneurysms secrete interleukin-6 into the circulation. J Vasc Surg 2007;45:350-6.
4. Golledge J, Clancy P, Jamrozik K, Norman PE. Obesity, adipokines, and abdominal aortic aneurysm: Health in Men study. Circulation 2007;116:2275-9.
5. Wanhainen A, Bergqvist D, Boman K, Nilsson TK, Rutegård J, Björck M. Risk factors associated with abdominal aortic aneurysm: a population-based study with historical and current data. J Vasc Surg 2005;41:390-6.
6. Powell JT, Muller BR, Greenhalgh RM. Acute phase proteins in patients with abdominal aortic aneurysms. J Cardiovasc Surg (Torino) 1987;28:528-30.

doi:10.1016/j.jvs.2009.03.049

Reply

Thank you for the opportunity to reply to this letter. There is increasing evidence for the paradigm shift of aneurysm aetiology from atherosclerosis to inflammatory, although a balance between the two is likely to reflect reality.[1,2] Consequently, an elevation of C-reactive protein (CRP) is to be expected if this is an accurate statement.

The inconsistency in the CRP findings by various researchers may be due to a number of factors, the first being the adequacy of study power. The results we obtained, where serum concentrations of CRP were found to be higher in abdominal aortic aneurysm (AAA) patients, with a gradation of amount according to AAA maximal diameter, were based upon a statistically sufficient study participant numbers.[3] All but one of the other studies included less than 100 AAA cases in the study cohort.[4-8] Second, the control selection is variable, ranging

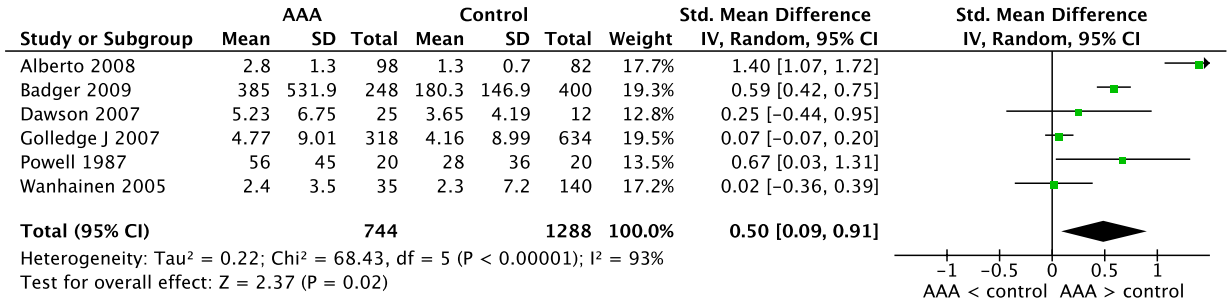

Fig. Standardized mean difference between cases with abdominal aortic aneurysm (AAA) and controls without AAA. *SD,* Standard deviation; *CI,* confidence interval.

from healthy controls to those deemed to be high-risk cardiovascular patients.[4-8] Clearly, this leads to a bias, since CRP is recognized as an independent marker of cardiovascular disease. Although complete control of this co-variable was not possible, we attempted to account for the presence of ischaemic heart disease in the study. Third, the analysis of multiple inflammatory markers concurrently obviously requires statistical compensation, to avoid a type 1 statistical error. Finally, our study was mainly to determine the influence of CRP genetic polymorphism on serum concentration and aneurysmal disease.[3]

Nonetheless, we cannot disregard the importance of this meta-analysis, given the higher level of evidence that it represents. Therefore, we concur that further research is required to confirm whether higher CRP concentration is associated with AAA.

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REFERENCES

1. Tilson MD. Aortic aneurysms and atherosclerosis. Circulation 1992;85:378-9.
2. Xu C, Zarins CK, Glagov S, Aneurysmal and occlusive atherosclerosis of the human abdominal aorta. J Vasc Surg 2001;33:91-6.
3. Badger SA, Soong CV, O'Donnell ME, Mercer C, Young IS, Hughes AE. C-reactive protein (CRP) elevation in patients with abdominal aortic aneurysm is independent of the most important CRP genetic polymorphism. J Vasc Surg 2009;49:178-84.
4. Alberto P, Maddalena G, Giuseppe G, Ilaria Q, Franci B, Campagna MS, et al. Prevalence of risk factors, coronary and systemic atherosclerosis in abdominal aortic aneurysm: comparison with high cardiovascular risk population. Vasc Health Risk Manag 2008;4:877-83.
5. Dawson J, Cockerill GW, Choke E, Belli AM, Loftus I, Thompson MM. Aortic aneurysms secrete interleukin-6 into the circulation. J Vasc Surg 2007;45:350-6.
6. Golledge J, Clancy P, Jamrozik K, Norman PE. Obesity, adipokines, and abdominal aortic aneurysm: Health in Men study. Circulation 2007;116:2275-9.
7. Wanhainen A, Bergqvist D, Boman K, Nilsson TK, Rutegård J, Björck M. Risk factors associated with abdominal aortic aneurysm: a population-based study with historical and current data. J Vasc Surg 2005;41:390-6.
8. Powell JT, Muller BR, Greenhalgh RM. Acute phase proteins in patients with abdominal aortic aneurysms. J Cardiovasc Surg (Torino) 1987;28:528-30.

doi:10.1016/j.jvs.2009.03.048